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**(54) USE OF INJECTABLE OR IMPLANTABLE BIOMATERIALS FOR FILLING OR BLOCKING
LUMENS AND VOIDS OF THE BODY**

INJEKTIERBARE ODER IMPLANTIERBARE BIOMATERIALIEN ZUM FÜLLEN ODER ABDECKEN
VON HOHLRÄUMEN UND LUMEN EINES KÖRPERS

UTILISATION DE BIOMATERIAUX INJECTABLES OU IMPLANTABLES POUR LE REMPLISSAGE
OU L'OBTURATION DE CONDUITS OU CAVITES DU CORPS

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Description

[0001] This invention is in the field of medical implants and injections. More particularly, it concerns complete or partial blocking, augmenting, sealing, or filling of various biological lumens and voids within the body of a patient, and provides for the use of a biomaterial in the manufacture of a medicament for such treatment.

BACKGROUND OF THE INVENTION

[0002] Lumens (or lumina) are the spaces in the interior of a tubular structure, such as an artery vein, intestine, Fallopian tube, trachea, and the like. In some instances, it may be desirable to augment, block, or fill these spaces to effect a preferred biological result. Further, some biological disease states, or treatments for such disease states, cause the formation of undesirable voids within various tissues or organs of the body.

[0003] One important lumen structure is the Fallopian tube, which is either of a pair of slender ducts that connect the uterus to the region of each of the ovaries in the female reproductive system. One existing form of birth control is the ligation of both tubes to prevent the movement of eggs or ova into the uterus, thus preventing pregnancy. Unfortunately, this method of birth control requires surgery and is irreversible unless the tubes are cut to remove the ligated portion and the remaining sections of the tubes are reconnected.

[0004] As a result of this surgery, the female patient is at greater risk of complications or of failures in the procedure. Further, this type of surgery is expensive and requires hospitalization. Therefore, other methods of birth control, which are less risky and more economical, are preferred.

SUMMARY OF THE INVENTION

[0005] A general method for completely or partially blocking, augmenting, sealing, or filling a biological lumen or void within the body of a patient comprises administering an effective amount of a biomaterial into the lumen or void. A particularly preferred method comprises administering by injection into the lumen or void an effective amount of a biomaterial composition comprising a biomaterial and a crosslinking agent before substantial crosslinking has occurred between the biomaterial and the crosslinking agent. Another preferred method comprises injecting an effective amount of a biomaterial composition comprising a particulate dehydrated crosslinked biomaterial and a nonaqueous carrier into the lumen or void. In an alternative method, one or more rods comprising an effective amount of a dehydrated biomaterial composition comprising a crosslinked biomaterial are implanted into the lumen or void.

[0006] To this end the invention provides the use of a biomaterial, formed from a polymer and a crosslinking agent in suspension or solution, in the manufacture of a medicament for use in a method for completely or partially blocking, augmenting, sealing or filling a biological lumen or void within the body of a patient comprising administering an effective amount of the biomaterial into the lumen or void, wherein the crosslinking agent is a hydrophilic crosslinking agent or a mixture of hydrophilic and hydrophobic crosslinking agents.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION**Preferred Biomaterials for Use in the Invention**

[0007] Biomaterials for use in the practice of the present invention must be biocompatible, essentially non-immunogenic, and injectable, threadable, or otherwise readily implantable. It is necessary that such biomaterials be in pharmaceutically pure form, or capable of being purified to be in pharmaceutically pure form, such that they can be incorporated into a human body without generating any significant immune response. Biomaterials for use in the invention should be capable of persisting at the site of placement for, preferably, three months or longer; more preferably, six months or longer; most preferably, one to two years or longer. It must be noted that the terms "biomaterial" and "biomaterial composition" are used interchangeably herein and are intended to encompass mixtures of the biomaterials described below.

[0008] Preferred biomaterials for use in the practice of the invention include, in general, all biocompatible, naturally occurring or synthetic polymers and, specifically, naturally occurring proteins such as collagen; various synthetic polypeptides such as poly(lysine); polysaccharides such as glycosaminoglycans; proteoglycans; and various polymeric hydrogels.

[0009] Proteins such as collagen, fibrin, and elastin are particularly suitable for use in the methods of the present invention. As used herein, the term "collagen" is intended to encompass collagen of any type, from any source, including, but not limited to, collagen extracted from tissue or produced recombinantly, collagen analogs, collagen derivatives, modified collagens, and denatured collagens such as gelatin.

[0010] Collagen is the major protein component of bone, cartilage, skin, and connective tissue in animals. Collagen

in its native form is typically a rigid, rod-shaped molecule approximately 300 nanometers (nm) long and 1.5nm in diameter. It is comprised of three collagen polypeptides which form a tight triple helix. The collagen polypeptides are characterized by a long midsection having the repeating sequence -Gly-X-Y-, where X and Y are often proline or hydroxyproline, bounded at each end by the "telopeptide" regions, which constitute less than about 5 percent (%) of the molecule. The telopeptide region of the collagen chains are typically responsible for the crosslinking between chains and for the immunogenicity of the protein.

[0011] In general, collagen from any source may be used in the practice of the present invention; for example, collagen may be extracted and purified from human or other mammalian sources, such as bovine or porcine corium and human placenta, or may be recombinantly or otherwise produced. The preparation of purified, substantially non-antigenic collagen in solution from bovine skin is basically a three-step process involving solubilization, enzyme treatment, and purification, as described in U.S. Patent Nos. 4,140,537 and 4,488,911. Commonly owned U.S. Patent No. 5 428 022 discloses methods of extracting and purifying collagen from the human placenta. Commonly owned, copending U.S. application Serial No. 08/183,648 discloses methods of producing recombinant human collagen in the milk of transgenic animals, including transgenic cows. The term "collagen" or "collagen material" as used herein refers to all forms of collagen, including those which have been processed or otherwise modified.

[0012] Collagen of any type, including, but not limited to, types I, II, III, IV, or any combination thereof, may be used, although type I is generally preferred. Either atelopeptide or telopeptide-containing collagen may be used; however, when collagen from a xenogeneic source, such as bovine collagen, is used, atelopeptide collagen is generally preferred, because of its reduced immunogenicity compared to telopeptide-containing collagen.

[0013] Collagen for use in the present invention may be in the fibrillar or nonfibrillar form. Fibrillar collagen has been shown to have increased persistence *in vivo* when compared to nonfibrillar collagen. However, the use of nonfibrillar collagen has certain advantages in the practice of the present invention, which will be discussed later in this section. The term "nonfibrillar collagen" as used herein is intended to encompass chemically modified collagens such as succinylated collagen and methylated collagen, both of which can be prepared according to the methods described in U.S. Patent No. 4,164,559.

[0014] Collagen for use in the practice of the invention may be either crosslinked or noncrosslinked. Noncrosslinked atelopeptide fibrillar collagen is commercially available from Collagen Corporation (Palo Alto, CA) at collagen concentrations of 35 mg/ml and 65 mg/ml under the trademarks Zyderm® I Collagen and Zyderm® II Collagen, respectively.

[0015] Collagen can be crosslinked using methods generally known in the art, such as by heat, radiation, or using conventional chemical crosslinking agents such as, for example, aldehydes, carbodiimides, epoxides, or imidazoles. U.S. Patent Nos. 4,582,640 and 4,642,117 disclose methods for preparing aldehyde-crosslinked collagens. Glutaraldehyde-crosslinked atelopeptide fibrillar collagen is commercially available at a collagen concentration of 35 mg/ml from Collagen Corporation under the trademark Zyplast® Collagen Implant.

[0016] Noncrosslinked and crosslinked collagens for use in the present invention are generally in aqueous suspension at a concentration between about 20 mg/ml to about 120 mg/ml, preferably, between about 30 mg/ml to about 90 mg/ml.

[0017] Denatured collagen, commonly known as gelatin, is also useful in the methods of the invention.

[0018] Various synthetically produced polypeptides may also be used in the practice of the invention. As used herein, the term "synthetic polypeptide" is intended to encompass polypeptides that have been produced using recombinant DNA techniques, as well as those produced by other methods of chemical synthesis. Poly(lysine), a synthetically produced polymer of the amino acid lysine (145 MW), is a particularly preferred synthetic polypeptide. Poly(lysine)s have been prepared having anywhere from 6 to about 4,000 primary amino groups, corresponding to molecular weights of about 870 to about 580,000. Poly(lysine)s of varying molecular weights are commercially available from Peninsula Laboratories, Inc. (Belmont, CA).

[0019] Glycosaminoglycans for use in the present invention include, without limitation, hyaluronic acid, chondroitin sulfate A, chondroitin sulfate C, dermatan sulfate, keratan sulfate, keratosulfate, chitin, chitosan, heparin, and derivatives or mixtures thereof. The preferred concentration of glycosaminoglycan will vary depending upon the specific glycosaminoglycan (or mixture of glycosaminoglycans) that is used.

[0020] Proteoglycans, such as decorin, biglycan, and fibromodulin, may also be used in the methods of the present invention. A proteoglycan consists of one or more glycosaminoglycan molecule bound to a core protein. In their native state within the body of an animal, many glycosaminoglycans are generally found in association with core proteins, *i. e.*, in the form of proteoglycans. However, certain glycosaminoglycans, such as hyaluronic acid, are not covalently bound to core proteins, but may be associated with proteoglycans through noncovalent interactions. Hyaluronic acid can also occur by itself, not associated with proteins.

[0021] Mixtures of various species of glycosaminoglycans or proteoglycans, various proteins, or mixtures of various glycosaminoglycans or proteoglycans with proteins may be used in the practice of the present invention.

[0022] A preferred polymeric hydrogel composition comprises a first synthetic polymer crosslinked using a second synthetic polymer, wherein the first synthetic polymer contains two or more nucleophilic groups, and the second syn-

thetic polymer contains two or more electrophilic groups capable of forming covalent bonds with the nucleophilic groups on the first synthetic polymer. The first synthetic polymer preferably contains two or more amino groups or thiol groups and is preferably a synthetic polymer containing two or more lysine residues (such as poly(lysine)); a synthetic polymer containing two or more cysteine residues; or a polyethylene glycol that has been modified to contain two or more amino or thiol groups. The second synthetic polymer is preferably a synthetic hydrophilic or hydrophobic polymer containing two or more succinimidyl groups. In order to form a crosslinked polymer network, the first synthetic polymer preferably contains three or more nucleophilic groups and the second synthetic polymer preferably contains three or more electrophilic groups. Nucleophilic groups on the first synthetic polymer react with electrophilic groups on the second synthetic polymer to form a covalently bound, crosslinked polymer network.

[0023] Particularly preferred biomaterial compositions for use in the practice of the invention comprise biomaterials, such as collagen or glycosaminoglycans, crosslinked using synthetic hydrophilic polymers, as disclosed in U.S. Patent Nos. 5,162,430; 5,324,775; and 5,328,955. Preferred synthetic hydrophilic polymers for use in the invention include functionally activated polyethylene glycols, more preferably, difunctionally activated polyethylene glycols. Particularly preferred difunctionally activated polyethylene glycols are disclosed in U.S. Patent No. 5,328,955.

[0024] As disclosed in commonly owned Patent U.S. Patent No. 5 510 418, glycosaminoglycans must generally be chemically modified by either deacetylation or desulfation (or both) in order to be capable of binding with synthetic hydrophilic polymer molecules. Deacetylation and desulfation can both be effected by the addition of a strong base, such as sodium hydroxide, to the glycosaminoglycan. Deacetylation and/or desulfation provides primary amino groups on the glycosaminoglycan which are capable of covalently binding with functional groups on synthetic hydrophilic polymers such as various polyethylene glycol derivatives. U.S. Patent No. 5 510 418 further discloses compositions wherein collagen and one or more species of glycosaminoglycan are crosslinked together using a synthetic hydrophilic polymer to form a heterogeneous conjugate.

[0025] A particularly preferred crosslinked biomaterial composition for use in the invention comprises a mixture of particulate crosslinked fibrillar collagen and non crosslinked fibrillar collagen which is subsequently crosslinked using a synthetic hydrophilic polymer, as disclosed in commonly owned, copending U.S. application Serial No. 08/344,040. The particulate crosslinked fibrillar collagen is preferably glutaraldehyde-crosslinked fibrillar collagen and preferably comprises between about 25 to about 95 percent, more preferably, between about 60 to about 80 percent by weight, of the final composition. The noncrosslinked fibrillar collagen preferably comprises between about 5 to about 75, more preferably, between about 20 to about 40 percent by weight, of the final composition. The particulate crosslinked fibrillar collagen and noncrosslinked fibrillar collagen are first combined, and then crosslinked together using a synthetic hydrophilic polymer, which is preferably a functionally activated polyethylene glycol.

[0026] Another preferred biomaterial composition is disclosed in commonly owned, copending U.S. application Serial No. 08/403,358. This application discloses a biomaterial composition that is crosslinked using a mixture of hydrophilic and hydrophobic crosslinking agents, which may be more resistant to enzymatic or hydrolytic degradation and, as such, display greater *in vivo* persistence than crosslinked biomaterial compositions prepared using only hydrophilic crosslinking agents. Preferred hydrophobic crosslinking agents include any hydrophobic polymer that contains, or can be chemically derivatized to contain, two or more succinimidyl groups. Commercially available hydrophobic crosslinking agents which contain two or more succinimidyl groups include: disuccinimidyl suberate, bis(sulfosuccinimidyl) suberate, dithiobis(succinimidylpropionate), bis(2-succinimidooxycarbonyloxy)ethyl sulfone, 3,3'-dithiobis(sulfosuccinimidyl)propionate, and their analogs and derivatives. Preferred hydrophilic crosslinking agents include synthetic hydrophilic polymers, particularly functionally activated polyethylene glycol derivatives, as discussed above. As such, the term "crosslinking agent", as used herein, is intended to encompass mixtures of crosslinking agents, such as a mixture of a synthetic hydrophilic polymer and a hydrophobic polymer containing two or more succinimidyl groups.

[0027] It is desirable for the biomaterial composition to be hydrophilic in order to allow the biomaterial to hydrate *in situ*, thereby creating a tight seal or strong adhesion between the collagen composition and the biological component of the body. Such an adhesion to the patient's own tissue will prevent leakage and allow complete blockage of the opening or void that needs to be blocked. The host tissue will also provide ingrowth over time, further strengthening the adhesion of the biomaterial to the tissue.

[0028] The hydrophilicity of the crosslinked biomaterial compositions discussed above can be increased by:

- (a) using nonfibrillar collagen (particularly, methylated collagen) as the biomaterial, which will require a higher molar ratio of synthetic hydrophilic polymer to collagen in order to achieve optimum crosslinking; or
- (b) using a higher molecular weight synthetic hydrophilic polymer to crosslink the biomaterial; or
- (c) crosslinking a mixture of a hydrophilic glycosaminoglycan, such as hyaluronic acid, and collagen together using a synthetic hydrophilic polymer.

[0029] As discussed in (b) above, and earlier in the specification, the use of nonfibrillar collagen, preferably methylated collagen, as the biomaterial may be advantageous in the present invention in that methylated collagen requires

a higher molar ratio of synthetic hydrophilic polymer to collagen to achieve optimum crosslinking, resulting in a biomaterial composition that is more hydrophilic and will hydrate to a greater degree *in situ* compared with compositions prepared using fibrillar collagen. Methods of crosslinking chemically derivatized nonfibrillar collagens, including methylated and succinylated collagens, using synthetic hydrophilic polymers are disclosed in commonly owned U.S. Patent No. 5 565 519.

[0030] Any of the above crosslinked biomaterial compositions can be dehydrated to form a solid product. As used herein, the term "dehydrated" means that the composition has been dried such that it contains substantially no unbound water. In one preferred embodiment, the biomaterial composition is dehydrated, chopped or cut such that it is present in particulate form, then suspended in a nonaqueous carrier for delivery by injection. The biomaterial composition is preferably extruded in the shape of a thin string before substantial crosslinking has occurred between the biomaterial and the crosslinking agent, allowed to finish crosslinking, then dehydrated. As described in U.S. Patent No. 5,308,889, the dehydrated crosslinked string is then chopped into small pieces before being suspended in a nonaqueous carrier in preparation for injection to a tissue site.

[0031] Alternatively, the biomaterial composition can be extruded into a rod-shaped mold prior to substantial crosslinking, removed from the mold after crosslinking is complete, then dehydrated (or allowed to dehydrate in the mold). One or more of the resulting dehydrated crosslinked biomaterial rods may be implanted in the body of a patient via catheter or using another appropriate method.

[0032] Following injection or implantation into the body of a patient, the dehydrated, crosslinked biomaterial compositions prepared as described above will quickly rehydrate to approximately five times their original dehydrated size. The exact amount of swelling will depend upon the hydrophilicity of the composition, which can be increased by varying the biomaterial and/or crosslinking agent as described above.

[0033] Biomaterial compositions for use in the present invention may further include one or more biocompatible fluid lubricants, such as, for example, hyaluronic acid, dextran-sulfate, dextran, succinylated noncrosslinked collagen, methylated noncrosslinked collagen, glycogen, glycerol, dextrose, maltose, triglycerides of fatty acids (such as corn oil, soybean oil, and sesame oil), and egg yolk phospholipid.

[0034] Various particulate materials may also be incorporated into biomaterial compositions for use in the invention. Suitable particulate materials include, without limitation, ceramic particles; particulate crosslinked or non-crosslinked fibrillar collagen; poly(lactic) acid (PLA), poly(glycolic) acid (PGA), and copolymers thereof (PLGA); calcium carbonate; calcium sulfate; gelatin beads; polytetrafluoroethylene beads; silicone rubber beads; beads of various hydrogel polymers (such as polyacrylonitrile-polyacrylamide hydrogels); silicon carbide beads; and glass beads.

[0035] U.S. Patent No. 4,803,075 discloses injectable compositions comprising an aqueous suspension of a particulate biomaterial in a biocompatible fluid lubricant. U.S. Patent No. 5,352,715 discloses an injectable composition comprising collagen and biocompatible ceramic (preferably, calcium phosphate; most preferably, tricalcium phosphate and/or hydroxyapatite) particles within the size range of 50 to 250 microns present in a pharmaceutically acceptable fluid carrier.

[0036] Biomaterial compositions for use in the invention may also incorporate one or more biologically active agent. The term "biologically active agent" or "active agent" as used herein refers to organic molecules which exert biological effects *in vivo*. Examples of active agents include, without limitation, enzymes, receptor antagonists or agonists, hormones, growth factors, autogenous bone marrow, antibiotics, antimicrobial agents, and antibodies. The term "active agent" is also intended to encompass various cell types which can be incorporated into the compositions of the invention. The term "active agent" is also intended to encompass combinations or mixtures of two or more active agents, as defined above.

[0037] Preferred active agents for use in methods of the present invention include growth factors, such as transforming growth factors (TGFs), fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), connective tissue activated peptides (CTAPs), osteogenic factors, and biologically active analogs, fragments, and derivatives of such growth factors. Members of the transforming growth factor (TGF) supergene family, which are multifunctional regulatory proteins, are particularly preferred. Members of the TGF supergene family include the beta transforming growth factors (for example, TGF- β 1, TGF- β 2, TGF- β 3); bone morphogenetic proteins (for example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9); heparin-binding growth factors (for example, fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF)); Inhibins (for example, Inhibin A, Inhibin B); growth differentiating factors (for example, GDF-1); and Activins (for example, Activin A, Activin B, Activin AB).

[0038] Members of the TGF supergene family are multifunctional regulatory proteins. For example, TGF- β 2, a 25,000 molecular weight homodimeric peptide, is capable of inducing site-specific healing responses by increasing collagen synthesis and deposition, as well as remodeling at sites of soft tissue repair. TGF- β 2 also activates osteoblasts to synthesize collagen *in vitro*. The most abundant sources of TGF- β 2 are bone and platelets.

[0039] Growth factors can be isolated from native or natural sources, such as from mammalian cells, or can be prepared synthetically, such as by recombinant DNA techniques or by various chemical processes. In addition, analogs,

fragments, or derivatives of these factors can be used, provided that they exhibit at least some of the biological activity of the native molecule. For example, analogs can be prepared by expression of genes altered by site-specific mutagenesis or other genetic engineering techniques.

[0040] The type of biologically active agent used will depend on the particular site and condition to be treated. The amount of biologically active agent to be included in the biomaterial composition will vary depending upon the type, concentration, and amount of biomaterial used; the sex, weight, age, and medical history of the patient; and the particular site and condition being treated. Typically, the weight ratio of biologically active agent to biomaterial will be in the range of from about 1:5000 to about 1:50,000.

[0041] Antibiotics or antimicrobial agents may be added to the biomaterial composition to reduce the potential for infection at the treatment site. Additionally, local anaesthetics may be used at the injection site to minimize discomfort. Any appropriate additive may be utilized as long as it is compatible with the biomaterial and the particular patient and disease state being treated.

[0042] Biologically active agents can be added to the biomaterial during preparation or just prior to treatment. It is preferred, but not required, that the biologically active agents be incorporated into the biomaterial such that the agents are released via a sustained-type delivery. In this way, the agents can be released into the tissue site and surrounding areas and exert their intended therapeutic effects over an extended period of time.

[0043] Biologically active agents may be incorporated into the biomaterial composition by admixture. Alternatively, the agents may be covalently linked to the biomaterial using a crosslinking agent such as a functionally activated polyethylene glycol, or affinity bound to the biomaterial using a binding ligand. Processes for covalently binding biologically active agents such as growth factors to collagen using a synthetic hydrophilic polymer, such as a functionally activated polyethylene glycol, are described in commonly assigned U.S. Patent No. 5,162,430. Processes for affinity binding biologically active agents to collagen via binding ligands such as heparin are disclosed in commonly owned U.S. Patent No. 5 693 341.

[0044] The invention allows methods to be carried out for completely or partially blocking, augmenting, sealing, or filling various lumens or voids within the body of a patient. As used herein, the term "lumen" is intended to encompass various hollow organs or vessels of the body, such as Fallopian tubes, veins, arteries, intestines, trachea, and the like. The term "void" is intended to encompass any hollow space created by congenital abnormalities, disease, aging, and/or surgery, such as extraction of tumors and other growth masses. As such, the term "void" encompasses lesions, fissures, fistulae, cysts, diverticulae, aneurysms, and any other undesirable void present in any tissue or organ of the body which may result from congenital abnormalities, disease, aging, or surgery. For example, the methods can be used to seal fissures or crevices within a tissue or structure (such as a vessel), or junctures between adjacent tissues or structures, to prevent the leakage of blood or other biological fluids.

[0045] According to the most general method, an effective amount of a biomaterial composition is administered to the site of a lumen or void within the body of a patient. The term "effective amount," as used herein, means the quantity of biomaterial needed to augment, block, or fill the biological structure of interest. The effective amount of biomaterial administered to a particular patient will vary depending upon a number of factors, including: the sex, weight, age, and general health of the patient; the patient's own ability to absorb or break down the biomaterial; the type, concentration, and consistency of the biomaterial; and the particular site and condition being treated. The biomaterial may be administered over a number of treatment sessions.

[0046] As described above, an effective amount of one or more biologically active agents, such as a wound healing agent, antibiotic, or antimicrobial agent, can be incorporated into the biomaterial composition. In this context, an "effective amount" refers to the amount of biologically active agent, antibiotic, or antimicrobial agent required to obtain the desired therapeutic effect, such as improved or accelerated healing of the defect or void, or prevention of infection at the site of administration.

[0047] As used herein, the term "effective amount," whether in reference to a biomaterial or biologically active agent, also refers to that amount of material which is pharmaceutically and physiologically acceptable to the particular patient undergoing treatment.

[0048] In a preferred method, the biomaterial composition is administered by injection to a lumen or void in need of treatment. In a particularly preferred method, a biomaterial (including mixtures of different biomaterials) and a crosslinking agent are mixed just prior to injection to the treatment site, then injected before substantial crosslinking has occurred between the biomaterial and the crosslinking agent. This allows the biomaterial composition to continue crosslinking *in situ* and prevents blockage of the syringe needle with gelled biomaterial. In addition, such *in situ* crosslinking may allow anchoring of the biomaterial to host tissue by covalently bonding with collagen molecules present within the host tissue. Preferred crosslinking agents for use in the practice of this method are synthetic hydrophilic polymers and mixtures of hydrophilic and hydrophobic crosslinking agents, as described in the previous section.

[0049] In an alternative method, crosslinked biomaterial compositions prepared as described in the previous section are molded into a desired shape, such as a rod or string, then dehydrated. The dehydrated biomaterial composition is then implanted into a lumen or void via catheter, endoscope, or other means. Once in contact with biological fluids in

the body of the patient, the dehydrated biomaterial rehydrates and swells in size to fill the lumen or void.

[0050] In yet another general method, a dehydrated crosslinked biomaterial composition, as described in the previous paragraph, is chopped or cut into small particulates, suspended in a nonaqueous carrier, then injected to fill a lumen or void in need of treatment.

5 [0051] The methods generally described above are especially useful for a reversible form of birth control or sterility in females, wherein the biomaterial is threaded, injected, or implanted, such that the Fallopian tubes are filled or blocked by the biomaterial, thereby preventing egg and/or sperm from passing through or around the biomaterial. Using this approach, pregnancy would be prevented since the ova or eggs located in the Fallopian tubes would not exit to the uterus and would not make contact with sperm. The blockage, and hence the sterility or birth control, is reversible by
10 removal of the biomaterial or resectioning of the tube after surgery, wherein the blocked portion of the tube is excised and the remaining portions of the tube are reconnected. It is preferable that the sections of the Fallopian tubes blocked with the biomaterial are those directly connected or closest to the uterus.

[0052] Administration of the biomaterial for this therapeutic indication can occur via catheter or via endoscopes, such as a fiberoptic scope, hysteroscope, and the like. See "Hysteroscopic Approaches for Tubal Closures," John J. Sciarra, Research Frontiers in Fertility Regulation, 1980, Chapter 26, pp. 270-286. Preferably, the biomaterial is injected into
15 the Fallopian tubes using a catheter, such as, for example, the Selective Salpingography Soft Torque™ Catheter, VS™ Recanalization Catheter, or VS™ Falloposcopy Catheter (all from Conceptus, Inc., San Carlos, CA).

[0053] The delivery of the biomaterial via injection or implantation provides a means to effectively target the biomaterial to a specific site or location, thereby localizing the biomaterial and minimizing systemic side effects. In addition,
20 the biocompatibility of the material minimizes any immunologic reaction of the patient to the biomaterial. Moreover, the administration of the biomaterial via implant or injection is minimally invasive and usually can be performed on an outpatient basis, resulting in a lower cost than other surgical forms of sterility or birth control. The procedure also eliminates patient compliance, since the patient need not follow any specific instructions or remember to ingest or insert other forms of birth control, such as pills, diaphragms, and the like. However, supplemental forms of birth control
25 can be utilized, if desired, especially those which prevent disease transmission.

[0054] The biomaterial and the methods of the invention also can be utilized for tracheal occlusions *for in utero* correction of fetal congenital defects, such as child congenital diaphragmatic *hernia* (CDH). See Longaker et al., "Maternal Outcomes After Open Fetal Surgery: A Review of the First 17 Human Cases," J. Amer. Med. Assoc., 265(6): 737-741 (1991). CDH primarily induces pulmonary hypoplasia, thereby lessening the ability of a newborn to adequately
30 exchange oxygen. The condition is typically diagnosed by ultrasound during pregnancy and is caused by the compression of the developing lungs by other internal organs, such as the intestine, stomach, and liver, due to the herniation of the diaphragm. The rupture of the diaphragm allows the internal organs to move into the chest cavity, restricting the development of the lungs, since there is less space for lung growth.

[0055] By occluding the fetal trachea, the intrapulmonary pressure gradually increases due to the fluid build-up in the lungs. This pressure increase propels the internal organs slowly from the chest cavity and allows full development
35 of the fetal lungs, preventing pulmonary hypoplasia.

[0056] It is desirable that the occlusion method be easily reversible at birth, so that the infant can breathe without difficulty. Fortunately, the umbilical connection between mother and child provides sufficient time to remove the occlusion before the infant must breathe on its own. It is important that the tracheal occlusion method be reproducible,
40 reliable, reversible, and atraumatic, thereby minimizing the risk to the mother and infant both at the time of occlusion and upon removal of the biomaterial, which causes the occlusion. Further, the cell lining of the trachea or the trachea itself must not be severely damaged.

[0057] Administration of the biomaterial to the fetal trachea can be via injection, using the ultrasound technique or fiberoptic scope for placement guidance. The biomaterial is placed within the trachea to completely fill it, forming a
45 column of material. Preferably, a suture or stitch is placed through the trachea to hold the biomaterial in place. Since the trachea will expand in size as the fetus matures, it is important to utilize a biomaterial that expands such that the trachea continues to be blocked and the biomaterial is not expelled. Therefore, the preferred biomaterial for this indication will be one that is strongly hydrophilic and can expand at a rate that is equal to the growth rate of the fetal trachea. Methods for increasing the hydrophilicity of a biomaterial composition are described in the previous section.

50 [0058] This method of administration minimizes the surgical risks to the mother and the fetus when compared to other occlusion approaches, such as physically tying off the trachea (see Longaker). It also allows for easy removal, since the biomaterial typically gels and solidifies *in situ* and can easily be removed with tweezers or similar instruments. This quick and easy removal process lessens the time of non-breathing for the newborn infant. In order to optimize the timing of the birth and to facilitate the biomaterial's removal, the delivery is typically by Caesarean section.

55 [0059] The invention also allows methods to be carried out for treating undesired lesions, fissures, diverticulae, cysts, fistulae, aneurysms, and any other undesirable voids present within the body of a patient, by administering a biomaterial to the site of these conditions. For example, the biomaterial can be injected, implanted, or threaded into fistula between viscera or into the opening or orifice from a viscus to the exterior of the patient's body. The biomaterial fills the defect

formed by these pathological states and stimulates fibroblast infiltration and healing, resulting in the ingrowth of tissue.

[0060] The biomaterial can be introduced by injection through a small gauge needle into one of the fistular orifices, filling all of the branches of the orifice and polymerizing or crosslinking *in situ*. Alternatively, dehydrated strings or rods of the materials (prepared as previously described) can be threaded into the lesions through an orifice or introduced by catheter. Various types of fistulae can be treated by this method and include anal fistulae, arteriovenous fistulae, bladder fistulae, carotid-cavernous fistulae, external fistulae, gastric fistulae, intestinal fistulae, parietal fistulae, salivary fistulae, vaginal fistulae, anorectal fistulae, and the like.

[0061] Diverticulae also can be treated. These abnormal physiological structures are pouches or sac openings from a tubular or saccular organ, such as the intestine, the bladder, and the like, and can be filled or augmented by the biomaterial. Cysts, which are abnormal sacs with a membrane lining containing gas, fluid, or semi-solid material, also can be filled, along with pseudocysts, which are an accumulation of fluid in a cyst-like locule, but without an epithelial or other membranous lining. Examples of cysts that can be treated include serous cysts, sebaceous cysts, dermoid cysts, bone cysts, and the like.

[0062] Another method allowed by this invention is the administration of a biomaterial to fill in whole, or in part, any void spaces formed as the result of surgical, chemical or biological removal of unnecessary or undesirable growths, fluids, cells, or tissues. The biomaterial can be locally administered at the site of the void, augmenting the remaining and surrounding tissue to aid in the healing process and to minimize infection. This augmentation is especially useful for void sites created after tumor excision, such as after breast cancer surgery, surgery for removal of tumorous connective tissue, bone or cartilage tissue, and the like.

[0063] For all the various therapeutic indications that can be treated by means of the invention, it is desirable to properly place the biomaterial in the bodily region of interest, such that the biomaterial either is held in place during the treatment, or held in place for a sufficient length of time to allow polymerization *in situ* for certain biomaterials. The biomaterial can be localized by the use of a clamp, balloon catheter, umbrella, surgical instrument, and the like. Injection of a biomaterial between a dual balloon catheter can be used to block the lumen anterior and posterior to the catheter tip.

[0064] Moreover, there are procedures in which the ultimate removal of the biomaterial is desired or necessary. Therefore, in those procedures, the biomaterial should be in a solid or semi-solid form at the time of removal. Removal can occur by physical means, such as surgery, or by mechanical means, such as pressure or suction. The biomaterial also can be pulled from a lumen using strings, wires, and the like, which are firmly embedded or attached to the biomaterial in order to permit complete removal.

[0065] An alternative method for removal is the *in vivo* degradation of the biomaterial, for example, by enzymes such as collagenase. The rate of degradation *in vivo* and eventual resorption by the body can be controlled by varying a number of factors including, without limitation, the type, concentration, and amount of biomaterial and/or crosslinking agent (if any) used. Higher concentration materials tend to have greater *in vivo* persistence. Crosslinked biomaterial compositions tend to persist *in vivo* longer than noncrosslinked formulations; tightly crosslinked biomaterials (i.e., those for which the concentration of the particular crosslinking agent employed has been optimized) tend to persist longer than more loosely crosslinked materials. When functionally activated polyethylene glycols are used as the crosslinking agent, those which incorporate ether linkages may persist longer *in vivo* than those incorporating ester linkages because of the greater resistance to hydrolysis of the ether linkages. Denatured biomaterials such as gelatin (denatured collagen) generally show the shortest *in vivo* lifetimes.

EXPERIMENTAL

[0066] The following experimental section is offered by way of example and not by limitation. The invention is described below in some detail for the purposes of clarity and understanding.

Example 1

(Guinea Pig Bladder Stress Test)

[0067] Crosslinked collagen rods were prepared as follows: Fibrillar collagen (65 mg/ml collagen concentration, obtained from Collagen Corporation, Palo Alto, CA) was mixed using syringe-to-syringe mixing with difunctionally activated SG-PEG (DSG-PEG, 3800 MW, obtained from Shearwater Polymers, Huntsville, AL) in a 1 to 10 molar ratio of collagen to DSG-PEG. The collagen/DSG-PEG reaction mixture was extruded into small diameter (- 3 mm inner diameter) tubing. The reaction mixture was incubated in the tubing and allowed to crosslink overnight at 37°C. The tubing was cut in half to dislodge the crosslinked collagen gel in the form of a long thread or rod, which was subsequently air-dried in a flow hood under tension to keep it straight.

[0068] A crosslinked collagen rod, prepared as described above, was inserted into each of the ureters of a guinea

pig cadaver and cut to size. Approximately 7 cc of water with fluroscein dye was introduced into the bladder via the urethra using a fine gauge needle, then the urethra was ligated beyond the needle insertion point to prevent leakage of the bladder. The filled bladder was viewed under ultraviolet light and it was observed that the crosslinked collagen rod was not dislodged and that the bladder did not leak. The ureter was used as a model for a cell-lined tubular structure, as may be found in a fistula.

Example 2

(Fetal Tracheal Occlusion with Crosslinked Collagen for Diaphragmatic Hernia)

[0069] Pregnant New Zealand white female rabbits were operated on at day 23 of the gestation period (term is 31 days). With the mother rabbit under general anaesthesia, the uterus was exposed and gestational sacs of individual fetuses identified. A diaphragmatic hernia was created in one fetus through a left thoracotomy by grasping the diaphragm with forceps and cutting it with fine scissors. The fetus was sewn up and returned to the uterus.

[0070] A similarly created diaphragmatic hernia was performed on a second fetus; however, this fetus had a tracheal occlusion. Occlusion was performed by a midline dissection of the fetal trachea and injection of a collagen suspension mixed with crosslinking agent through a 25-gauge needle directly into the trachea on the lung side of the dissection. The second fetus was sewn up and returned to the uterus.

[0071] A third fetus underwent tracheal occlusion without creation of a diaphragmatic hernia. The remaining fetuses were left to develop in the uterus without surgery.

[0072] After operation on the fetuses, the uterus was sewn closed and gestation continued until day 30, at which time the fetuses were sacrificed.

[0073] Individual fetal wet lung weight and total body weight was measured, and the fetal wet lung weight to total body weight ratio (LW/BW) was calculated, as shown in Table 1, below.

Table 1.

Fetal Wet Lung Weight and Total Body Weight			
Animal	Wet Lung Weight(g)	Body Weight (g)	LW/BW
DHTO	0.566	17.246	0.0328
DH	0.238	11.580	0.0206
NO	0.271	11.868	0.0271
DHTO = Diaphragmatic Hernia and Tracheal Occlusion with crosslinked collagen			
DH = Diaphragmatic Hernia only			
NO = No Operation			

[0074] The results presented in Table 1 show that the crosslinked collagen was able to occlude the trachea, resulting in normal lung development in the fetal rabbit.

Claims

1. Use of a biomaterial, formed from a polymer and a cross-linking agent in suspension or solution, in the manufacture of a medicament for use in a method for completely or partially blocking, augmenting, sealing, or filling a biological lumen or void within the body of a patient comprising administering an effective amount of the biomaterial into the lumen or void, wherein the cross-linking agent is a hydrophillic crosslinking agent, or a mixture of hydrophillic and hydrophobic crosslinking agents.
2. The use according to claim 1, wherein the polymer is a polymeric hydrogel, a protein, a synthetic polypeptide, a glycosaminoglycan, a proteoglycan, or mixtures thereof.
3. The use according to claim 2, wherein the polymer is in the crosslinked state in the administrable medicament.
4. The use according to claim 2, wherein the biomaterial is administered before substantial crosslinking of the polymer has occurred.

5. The use according to claim 3 or 4, wherein the polymer is a protein.
6. The use according to claim 5, wherein the protein is collagen.
- 5 7. The use according to claim 6, wherein the collagen is fibrillar collagen.
8. The use according to claim 7, wherein the collagen comprises a mixture of particulate crosslinked fibrillar collagen and noncrosslinked fibrillar collagen.
- 10 9. The use according to claim 8, wherein the particulate crosslinked fibrillar collagen comprises between 25% to 95% and the noncrosslinked fibrillar collagen comprises between 5% to 75% by weight of the biomaterial.
10. The use according to claim 6, wherein the collagen is nonfibrillar collagen.
- 15 11. The use according to claim 10, wherein the nonfibrillar collagen is methylated collagen.
12. The use according to claim 6, wherein the collagen is denatured collagen.
13. The use according to claim 3 or 4, wherein the polymer is a glycosaminoglycan which is hyaluronic acid, chondroitin sulfate A, chondroitin sulfate C, dermatan sulfate, keratan sulfate, keratosulfate, chitin, chitosan, heparin, or a derivative thereof.
- 20 14. The use according to claim 13, wherein the glycosaminoglycan is hyaluronic acid.
- 25 15. The use according to claim 2, wherein the polymer comprises a crosslinked mixture of collagen and one or more species of glycosaminoglycan.
16. The use according to claim 1, wherein the crosslinking agent is an aldehyde, carbodiimide, epoxide or imidazole.
- 30 17. The use according to claim 1, wherein the crosslinking agent is a synthetic hydrophilic polymer.
18. The use according to claim 17, wherein the synthetic hydrophilic polymer is a functionally activated polyethylene glycol.
- 35 19. The use according to claim 18, wherein the synthetic hydrophilic polymer is a difunctionally activated polyethylene glycol.
20. The use according to any preceding claim, wherein the biomaterial is formed from the polymer and a mixture of hydrophilic and hydrophobic crosslinking agents.
- 40 21. The use according to claim 20, wherein the hydrophobic crosslinking agent is a hydrophobic polymer which contains two or more succinimidyl groups prior to bonding with the biomaterial.
22. The use according to claim 21, wherein the hydrophobic polymer is disuccinimidyl suberate, bis (sulfosuccinimidyl) suberate, dithiobis (succinimidylpropionate), bis (2-succinimidooxycarbonyloxy) ethyl sulfone, 3, 3'-dithiobis (sulfosuccinimidyl) propionate, or an analog or derivative thereof.
- 45 23. The use according to any preceding claim, wherein the biomaterial is a polymeric hydrogel which comprises a first synthetic polymer crosslinked using a second synthetic polymer, wherein the first synthetic polymer contains two or more nucleophilic groups, and the second synthetic polymer contains two or more electrophilic groups capable of forming covalent bonds with the nucleophilic groups on the first synthetic polymer.
- 50 24. The use according to any preceding claim, wherein the biomaterial is formed additionally from one or more biocompatible fluid lubricants selected from hyaluronic acid, dextran sulfate, dextran, succinylated noncrosslinked collagen, methylated noncrosslinked collagen, glycogen, glycerol, dextrose, maltose, triglycerides of fatty acids, and egg yolk phospholipid; and/or the biomaterial is formed additionally from a particulate material selected from ceramic particles, crosslinked or noncrosslinked particulate fibrillar collagen, gelatin beads, polytetrafluoroethylene beads, silicone rubber beads, beads of various hydrogel polymers, silicon carbide beads, glass beads, and mixtures
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thereof; and/or the biomaterial is formed additionally from an effective amount of one or more biologically active agents.

25. The use according to claim 24, wherein the biologically active agents are selected from wound healing agents, antibiotics, and antimicrobial agents.
26. The use according to claim 25, wherein the biologically active agent is a wound healing agent selected from transforming growth factors (TGFs), fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), connective tissue activated peptides (CTAPs), osteogenic factors, and biologically active analogs, fragments, and derivatives thereof.
27. The use according to any one of the preceding claims, wherein the lumen is a Fallopian tube, a trachea, an artery, a vein, or an intestine; and/or the void is an aneurysm, lesion, fissure, fistula, cyst or a diverticulae of any organ.
28. The use according to claim 1, wherein the void is present in the body of the patient as a result of surgical, chemical, or biological removal of unnecessary or undesirable growths, fluids, cells or tissues.
29. The use according to claim 3, wherein the crosslinked biomaterial is dehydrated, and after administration rehydrates and swells in size thereby allowing the biomaterial to block or fill the lumen or void.
30. The use according to claim 29, wherein the dehydrated crosslinked biomaterial is present in particulate form, suspended in a pharmaceutically acceptable nonaqueous carrier, and administered by injection into the lumen or void.
31. The use according to claim 29, wherein the dehydrated crosslinked biomaterial is present in rod form for administering into the lumen or void via a catheter or an endoscope.
32. The use according to any of claims 1, 2, 3 and 5-31, wherein the medicament is for use by injection or implantation, after which the biomaterial rehydrates and swells in size thereby allowing the biomaterial to partially or totally block or fill the lumen or void.
33. The use according to any of claims 1, 2 and 4 -28, wherein the medicament is for use by injection and wherein the medicament is administered before substantial crosslinking has occurred.

Patentansprüche

1. Verwendung eines Biomaterials, gebildet aus einem Polymer und einem Vernetzungsmittel in Suspension oder Lösung, bei der Herstellung eines Arzneimittels zur Verwendung in einem Verfahren zum vollständigen oder teilweisen Blockieren, Vergrößern, Verschließen oder Füllen eines biologischen Lumens oder Hohlraums im Körper eines Patienten umfassend das Verabreichen einer wirksamen Menge des Biomaterials in das Lumen oder den Hohlraum, wobei das Vernetzungsmittel ein hydrophiles Vernetzungsmittel oder eine Mischung von hydrophilen und hydrophoben Vernetzungsmitteln ist.
2. Die Verwendung gemäß Anspruch 1, worin das Polymer ein polymeres Hydrogel, ein Protein, ein synthetisches Polypeptid, ein Glucosaminoglycan, ein Proteoglycan oder Mischungen davon ist.
3. Die Verwendung gemäß Anspruch 2, worin das Polymer in dem verabreichbaren Arzneimittel in dem vernetzten Zustand vorliegt.
4. Die Verwendung gemäß Anspruch 2, worin das Biomaterial verabreicht wird, bevor eine wesentliche Vernetzung des Polymers stattgefunden hat.
5. Die Verwendung gemäß Anspruch 3 oder 4, worin das Polymer ein Protein ist.
6. Die Verwendung gemäß Anspruch 5, worin das Protein Collagen ist.
7. Die Verwendung gemäß Anspruch 6, worin das Collagen fibrilläres Collagen ist.

8. Die Verwendung gemäß Anspruch 7, worin das Collagen eine Mischung von partikulärem vernetztem fibrillärem Collagen und nichtvernetztem fibrillärem Collagen umfasst.
- 5 9. Die Verwendung gemäß Anspruch 8, worin das partikuläre vernetzte fibrilläre Collagen zwischen 25 % bis 95 % und das nichtvernetzte fibrilläre Collagen zwischen 5 % bis 75 Gew.-% des Biomaterials umfasst.
10. Die Verwendung gemäß Anspruch 6, worin das Collagen nichtfibrilläres Collagen ist.
- 10 11. Die Verwendung gemäß Anspruch 10, worin das nichtfibrilläre Collagen methyliertes Collagen ist.
12. Die Verwendung gemäß Anspruch 6, worin das Collagen denaturiertes Collagen ist.
13. Die Verwendung gemäß Anspruch 3 oder 4, worin das Polymer ein Glucosaminoglycan darstellt, das Hyaluronsäure, Chondroitinsulfat A, Chondroitinsulfat C, Dermatan-sulfat, Keratansulfat, Keratosulfat, Chitin, Chitosan, Heparin oder ein Derivat davon ist.
- 15 14. Die Verwendung gemäß Anspruch 13, worin das Glucosaminoglycan Hyaluronsäure ist.
15. Die Verwendung gemäß Anspruch 2, worin das Polymer eine vernetzte Mischung von Collagen und einer oder mehrerer Spezies von Glucosaminoglycan umfasst.
- 20 16. Die Verwendung gemäß Anspruch 1, worin das Vernetzungsmittel ein Aldehyd, Carbodiimid, Epoxid oder Imidazol ist.
- 25 17. Die Verwendung gemäß Anspruch 1, worin das Vernetzungsmittel ein synthetisches hydrophiles Polymer ist.
18. Die Verwendung gemäß Anspruch 17, worin das synthetische hydrophile Polymer ein funktionell aktiviertes Polyethylenglycol ist.
- 30 19. Die Verwendung gemäß Anspruch 18, worin das synthetische hydrophile Polymer ein difunktionell aktiviertes Polyethylenglycol ist.
20. Die Verwendung gemäß einem der vorhergehenden Ansprüche, worin das Biomaterial aus dem Polymer und einer Mischung von hydrophilen und hydrophoben Vernetzungsmitteln gebildet wird.
- 35 21. Die Verwendung gemäß Anspruch 20, worin das hydrophobe Vernetzungsmittel ein hydrophobes Polymer ist, das vor dem Binden mit dem Biomaterial zwei oder mehr Succinimidylgruppen enthält.
- 40 22. Die Verwendung gemäß Anspruch 21, worin das hydrophobe Polymer ein Disuccinimidylsuberat, Bis(sulfosuccinimidyl)suberat, Dithiobis(succinimidylpropionat), Bis(2-succinimidooxycarbonyloxy)ethylsulfon, 3,3'-Dithiobis(sulfosuccinimidyl)-propionat oder ein Analogon oder ein Derivat davon ist.
- 45 23. Die Verwendung gemäß einem der vorhergehenden Ansprüche, worin das Biomaterial ein polymeres Hydrogel ist, das ein erstes synthetisches Polymer umfasst, das unter Verwendung eines zweiten synthetischen Polymers vernetzt wird, wobei das erste synthetische Polymer zwei oder mehr nukleophile Gruppen enthält und das zweite synthetische Polymer zwei oder mehr elektrophile Gruppen enthält, die im Stande sind, mit den nukleophilen Gruppen auf dem ersten synthetischen Polymers kovalente Bindungen zu bilden.
- 50 24. Die Verwendung gemäß einem der vorhergehenden Ansprüche, worin das Biomaterial zusätzlich aus einem oder mehreren biokompatiblen flüssigen Gleitmitteln besteht, ausgewählt aus Hyaluronsäure, Dextran-sulfat, Dextran, succinyliertes nichtvernetztes Collagen, methyliertes nichtvernetztes Collagen, Glycogen, Glycerol, Dextrose, Maltose, Fettsäuretriglyceride und Eigelbphospholipid; und/oder das Biomaterial zusätzlich aus einem partikulärem Material gebildet wird, ausgewählt aus keramischen Teilchen, vernetztem oder nichtvernetztem partikulärem fibrillärem Collagen, Gelatinekügelchen, Polytetrafluorethylenkügelchen, Silikonkautschukkügelchen, Kügelchen von verschiedenen Hydrogelpolymeren, Siliciumcarbidkügelchen, Glaskügelchen und Mischungen davon; und/oder
- 55 das Biomaterial zusätzlich aus einer wirksamen Menge von einem oder mehreren biologisch wirksamen Mitteln gebildet wird.

25. Die Verwendung gemäß Anspruch 24, worin die biologisch wirksamen Mittel ausgewählt werden aus Mitteln zur Wundheilung, Antibiotika und antimikrobiellen Mitteln.
- 5 26. Die Verwendung gemäß Anspruch 25, worin das biologisch wirksame Mittel ein Mittel zur Wundheilung ist, ausgewählt aus transformierenden Wachstumsfaktoren (transforming growth factors, TGFs), Fibroblasten-Wachstumsfaktoren (fibroblast growth factors, FGFs), Plättchen-abhängigen Wachstumsfaktoren (platelet derived growth factors, PDGFs), epidermale Wachstumsfaktoren (epidermal growth factors, EGFs), Bindegewebe-aktivierte Peptide (connective tissue activated peptides, CTAPs), osteogene Faktoren und biologisch wirksame Analoga, Fragmente und Derivate davon.
- 10 27. Die Verwendung gemäß einem der vorhergehenden Ansprüche, worin das Lumen ein Eileiter, eine Luftröhre, eine Arterie, eine Vene oder ein Darm ist; und/oder der Hohlraum ein Aneurysma, Wunde, Fissur, Fistel, Zyste oder ein Divertikel irgendeines Organs ist.
- 15 28. Die Verwendung gemäß Anspruch 1, worin der Hohlraum im Körper eines Patienten als ein Ergebnis einer chirurgischen, chemischen oder biologischen Entfernung von unnötigen oder unerwünschten Verwachsungen, Fluiden, Zellen oder Geweben vorliegt.
- 20 29. Die Verwendung gemäß Anspruch 3, worin das vernetzte Biomaterial dehydratisiert wird und nach der Verabreichung rehydratisiert und größtmäßig anschwillt, wodurch ermöglicht wird, dass das Biomaterial das Lumen oder den Hohlraum blockiert oder füllt.
- 25 30. Die Verwendung gemäß Anspruch 29, worin das dehydratisierte vernetzte Biomaterial in partikulärer Form vorliegt, in einem pharmazeutisch verträglichen nichtwässrigen Träger suspendiert, und durch Injektion in das Lumen oder den Hohlraum verabreicht wird.
31. Die Verwendung gemäß Anspruch 29, worin das dehydratisierte vernetzte Biomaterial in Stäbchenform für eine Verabreichung in das Lumen oder den Hohlraum über einen Katheder oder ein Endoskop vorliegt.
- 30 32. Die Verwendung gemäß einem der Ansprüche 1, 2, 3 und 5-31, worin das Arzneimittel für eine Anwendung mittels Injektion oder Implantation ist, wonach das Biomaterial rehydratisiert und größtmäßig anschwillt, wodurch ermöglicht wird, dass das Biomaterial teilweise oder vollständig das Lumen oder den Hohlraum blockiert oder füllt.
- 35 33. Die Verwendung gemäß einem der Ansprüche 1, 2 und 4-28, worin das Arzneimittel für eine Anwendung mittels Injektion ist und worin das Arzneimittel verabreicht wird, bevor eine wesentliche Vernetzung stattgefunden hat.

Revendications

- 40 1. Utilisation d'un biomatériau, formé à partir d'un polymère et d'un agent de réticulation en suspension ou en solution, dans la fabrication d'un médicament destiné à être utilisé dans un procédé de blocage, d'augmentation, de scellement ou de remplissage partiel ou total d'une lumière ou d'une cavité biologique dans le corps d'un patient comprenant l'administration d'une quantité efficace du biomatériau dans la lumière ou dans la cavité, dans lequel l'agent de réticulation est un agent de réticulation hydrophile, ou un mélange d'agents de réticulation hydrophiles et hydrophobes.
- 45 2. Utilisation selon la revendication 1, dans laquelle le polymère est un hydrogel polymère, une protéine, un polypeptide synthétique, un glycosaminoglycane, un protéoglycane, ou des mélanges de ceux-ci.
- 50 3. Utilisation selon la revendication 2, dans laquelle le polymère est à l'état réticulé dans le médicament administrable.
4. Utilisation selon la revendication 2, dans laquelle le biomatériau est administré avant qu'une réticulation substantielle du polymère se soit produite.
- 55 5. Utilisation selon la revendication 3 ou 4, dans laquelle le polymère est une protéine.
6. Utilisation selon la revendication 5, dans laquelle la protéine est le collagène.

7. Utilisation selon la revendication 6, dans laquelle le collagène est du collagène fibrillaire.
8. Utilisation selon la revendication 7, dans laquelle le collagène comprend un mélange de collagène fibrillaire réticulé particulaire et de collagène fibrillaire non réticulé.
- 5 9. Utilisation selon la revendication 8, dans laquelle le collagène fibrillaire réticulé particulaire comprend entre 25 % et 95 % et le collagène fibrillaire non réticulé comprend entre 5 % et 75 % en poids du biomatériau.
- 10 10. Utilisation selon la revendication 6, dans laquelle le collagène est du collagène non fibrillaire.
11. Utilisation selon la revendication 10, dans laquelle le collagène non fibrillaire est du collagène méthylé.
12. Utilisation selon la revendication 6, dans laquelle le collagène est du collagène dénaturé.
- 15 13. Utilisation selon la revendication 3 ou 4, dans laquelle le polymère est un glycosaminoglycane qui est l'acide hyaluronique, la chondroïtine sulfate A, la chondroïtine sulfate C, le dermatane sulfate, le keratane sulfate, le keratosulfate, la chitine, la chitosane, l'héparine, ou un dérivé de ceux-ci.
- 20 14. Utilisation selon la revendication 13, dans laquelle le glycosaminoglycane est l'acide hyaluronique.
15. Utilisation selon la revendication 2, dans laquelle le polymère comprend un mélange réticulé de collagène et d'une ou plusieurs espèces de glycosaminoglycane.
- 25 16. Utilisation selon la revendication 1, dans laquelle l'agent de réticulation est un aldéhyde, un carbodiimide, un époxyde ou un imidazole.
17. Utilisation selon la revendication 1, dans laquelle l'agent de réticulation est un polymère hydrophile synthétique.
- 30 18. Utilisation selon la revendication 17, dans laquelle le polymère hydrophile synthétique est un polyéthylène glycol fonctionnellement activé.
19. Utilisation selon la revendication 18, dans laquelle le polymère hydrophile synthétique est un polyéthylène glycol di-fonctionnellement activé.
- 35 20. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le biomatériau est formé à partir du polymère et d'un mélange d'agents de réticulation hydrophiles et hydrophobes.
21. Utilisation selon la revendication 20, dans laquelle l'agent de réticulation hydrophobe est un polymère hydrophobe qui contient un ou plusieurs groupes succinimidydes préalablement à la liaison avec le biomatériau.
- 40 22. Utilisation selon la revendication 21, dans laquelle le polymère hydrophobe est disuccinimidyl suberate, bis(sulfosuccinimidyl)suberate, dithiobis (succinimidylpropionate), bis(2-succinimidooxycarbonyloxy)éthyl sulfone, 3,3'-dithiobis(sulfosuccinimidyl)propionate, ou un analogue ou un dérivé de ceux-ci.
- 45 23. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le biomatériau est un hydrogel polymère qui comprend un premier polymère synthétique réticulé à l'aide d'un second polymère synthétique, dans lequel le premier polymère synthétique contient deux groupes nucléophiles ou plus, et le second polymère synthétique contient deux groupes électrophiles ou plus capables de former des liaisons covalentes avec les groupes nucléophiles sur le premier polymère synthétique.
- 50 24. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le biomatériau est de plus formé à partir d'un ou plusieurs lubrifiants liquides biocompatibles choisis parmi l'acide hyaluronique, le dextrane sulfate, le dextrane, le collagène succinylé non réticulé, le collagène méthylé non réticulé, le glycogène, le glycérol, le dextrose, le maltose, les triglycérides des acides gras, un phospholipide de jaune d'oeuf ; et/ou le biomatériau est de plus formé à partir d'un matériau particulaire choisi parmi des particules céramiques, du collagène fibrillaire particulaire réticulé ou non réticulé, des billes de gélatine, des billes de polytétrafluoroéthylène, des billes de caoutchouc de silicone, des billes de divers hydrogels polymères, des billes de carbure de silicium, des billes de verre, et des mélanges de ceux-ci ; et/ou le biomatériau est de plus formé à partir d'une quantité efficace d'un ou plusieurs
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agents biologiquement actifs.

- 5
25. Utilisation selon la revendication 24, dans laquelle les agents biologiquement actifs sont choisis parmi des agents cicatrisants de plaie, des antibiotiques et des agents antimicrobiens.
- 10
26. Utilisation selon la revendication 25, dans laquelle l'agent biologiquement actif est un agent cicatrisant de plaie choisi parmi des facteurs de croissance transformants (TGF), des facteurs de croissance de fibroblastes (FGF), des facteurs de croissance dérivés des plaquettes (PDGF), des facteurs de croissance de l'épiderme (EGF), des peptides activés du tissu conjonctif (CTAP), des facteurs ostéogéniques, et les analogues, fragments et dérivés biologiquement actifs de ceux-ci.
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27. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la lumière est une trompe de Fallope, une trachée, une artère, une veine, ou un intestin ; et/ou la cavité est un anévrisme, une lésion, une fissure, une fistule, un kyste ou un diverticule de n'importe quel organe.
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28. Utilisation selon la revendication 1, dans laquelle la cavité est présente dans le corps du patient à la suite du retrait chirurgical, chimique ou biologique de grossiers, liquides, cellules ou tissus inutiles ou indésirables.
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29. Utilisation selon la revendication 3, dans laquelle le biomatériau réticulé est déshydraté, et après administration il se réhydrate et gonfle en taille de ce fait permettant que le biomatériau bloque ou remplisse la lumière ou la cavité.
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30. Utilisation selon la revendication 29, dans laquelle le biomatériau réticulé déshydraté est présent sous forme particulaire, mis en suspension dans un support non aqueux acceptable sur le plan pharmaceutique, et administré par injection dans la lumière ou la cavité.
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31. Utilisation selon la revendication 29, dans laquelle le biomatériau réticulé déshydraté est présent sous forme de tige pour une administration dans la lumière ou dans la cavité par l'intermédiaire d'un cathéter ou d'un endoscope.
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32. Utilisation selon l'une quelconque des revendications 1, 2, 3 et 5 à 31, dans laquelle le médicament est destiné à être utilisé par injection pour par implantation, après quoi le biomatériau se réhydrate et gonfle en taille de ce fait permettant que le biomatériau bloque ou remplisse partiellement ou totalement la lumière ou la cavité.
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33. Utilisation selon l'une quelconque des revendications 1, 2 et 4 à 28, dans laquelle le médicament est destiné à être utilisé par injection et dans laquelle le médicament est administré avant qu'une réticulation substantielle se soit produite.
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